

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID#: D050008

DATE: March 31, 2006

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THROUGH: Rosemary Johann-Liang, M.D., Deputy Director
for
Mark Avigan, M.D., C.M., Director
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SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Gemcitabine (Gemzar)
Pediatric Exclusivity Approval Date: 1/27/2005

1. Executive Summary

The Adverse Event Reporting System (AERS) database was searched for reports of adverse events (serious and non-serious) occurring with the use of gemcitabine in pediatric patients. From the date of FDA approval, 5/15/1996, to the "data lock" date of 2/27/2006, AERS contained 10,713 cases for gemcitabine (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 0.4% of the total (48/10,713).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, 1/27/2005 to 1/27/2006. We used an AERS data lock date of 2/27/2006 to allow time for reports received up to 1/27/2006 to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received 1501 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 0.6% of the total number of cases (9/1501). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

During the pediatric exclusivity period, five unduplicated pediatric cases associated with gemcitabine were reported to AERS. One case reported death as an outcome due to disease progression. Most of the remaining cases reported labeled adverse events, including cellulitis, pneumonitis, pancytopenia¹ and hepatotoxicity. One case reported an unlabeled adverse event, mucositis, an adverse event commonly associated with chemotherapy.

An additional search of AERS was performed to identify all fatal pediatric cases associated with gemcitabine before the pediatric exclusivity period. This search yielded one other unduplicated fatal pediatric case. This case described a patient with acute lymphoblastic leukemia with fever, leg pain, decreased white blood cells, hematemesis, epistaxis, refractory thrombocytopenia and acute respiratory distress. The family of this patient requested comfort measures only and she died 2 days later (cause of death not specified). Although these adverse events had a temporal relationship to the administration of gemcitabine, most of the events were labeled events for gemcitabine in a heavily pretreated refractory patient. Unlabeled events included epistaxis and hematemesis, clinical manifestations commonly seen in cancer patients with thrombocytopenia.

This review did not identify any notable or unexpected safety concerns with the use of gemcitabine in pediatric patients. We note that the pediatric patients in this case series were all adolescents. DDRE continues to routinely monitor reports of adverse events with the use of gemcitabine in pediatric patients.

2. Products, Indications, Pediatric Labeling and Pediatric Filing History

2.1 Gemcitabine Products

Gemcitabine is supplied in the U.S. in:

*200mg white, lyophilized powder in a 10-ml sterile single use vial
1gm white, lyophilized powder in a 50-ml size sterile single use vial*

2.2 Gemcitabine Approved Indications

Gemcitabine is approved for the following indications:

Breast Cancer: Gemzar in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

Non-Small Cell Lung Cancer: Gemzar is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.

¹ Labeled for myelosuppression

Pancreatic Cancer: Gemzar is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemzar is indicated for patients previously treated with 5-FU.

2.3 Gemcitabine Pediatric Labeling

The labeling for gemcitabine includes the following information concerning pediatric patients.

The effectiveness of Gemzar in pediatric patients has not been demonstrated. Gemzar was evaluated in a Phase 1 trial in pediatric patients with refractory leukemia and determined that the maximum tolerated dose was 10 mg/m²/min for 360 minutes three times weekly followed by a one week rest period. Gemzar was also evaluated in a Phase 2 trial in patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) using 10 mg/m²/min for 360 minutes three times weekly followed by a one week rest period. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation, which were similar to those reported in adults. No meaningful clinical activity was observed in this Phase 2 trial.

2.4 Pediatric Filing History

A formal Written Request (WR) for pediatric studies of gemcitabine was issued to Eli Lilly & Company on January 9, 2001 and reissued July 2, 2002. Amendments were made to the WR on December 13, 2002 and October 1, 2003. The sponsor completed the following studies:

- A phase 1 dose finding study with the primary endpoint of maximum tolerated dose and secondary endpoint of pharmacokinetics, with measurement of gemcitabine blood concentrations, clearance, and distribution in body compartments
- A phase 2 study with a primary endpoint of complete response rate

These studies fulfilled the requirements of the WR and pediatric exclusivity was granted January 27, 2005. A supplemental new drug application was submitted January 11 and 17, 2005 to provide for revisions to the *Pediatric Patients* subsection of the PRECAUTIONS section of the package insert to reflect the data from these studies. This application was approved April 26, 2005.

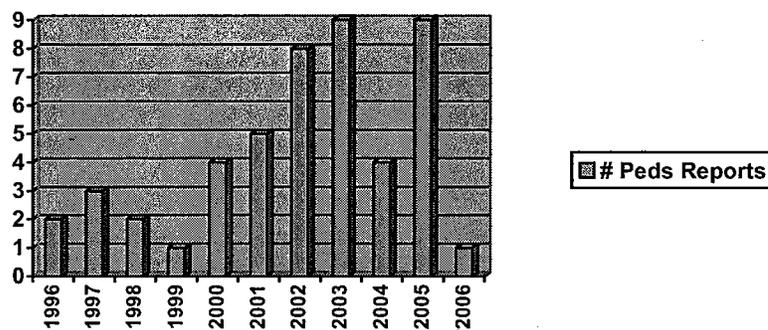
3. AERS Search Results: Gemcitabine

3.1 Count of Reports: AERS Search including all sources - U.S. & foreign from marketing approval date (Table 1)

Table 1: Crude counts ¹ of AERS Reports for all sources from marketing approval date (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	9463 (5843)	8972 (5398)	2970 (1743)
Pediatrics (0-16 yrs.)	48 (35)	46 (34)	7 ³ (5 ³)
Age unknown (Null values)	1202 (914)	1038 (775)	496 (411)
Total	10713 (6792)	10056 (6207)	3473 (2159)

¹ May include duplicates
² Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.
³ Crude count. Actual number after removing duplicate and incorrectly coded reports is 2.

Figure 1: Reporting trend for pediatric reports from approval date



*includes reports until 2/27/2006

3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)

Table 2: Crude counts ¹ of AERS Reports for all sources from date Pediatric Exclusivity was granted (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	1385 (801)	1333 (756)	373 (194)
Pediatrics (0-16 yrs)	9 ³ (9 ³)	9 ³ (9 ³)	1 (1)
Age unknown (Null Values)	107 (57)	100 (52)	28 (11)
Total	1501 (867)	1442 (817)	402 (206)

¹ May include duplicates
² Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.
³ Crude count. Actual number after removing duplicate and incorrectly coded reports is 5.

4. Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.

4.1 Case Characteristics:

Table 3 below describes the characteristics of the pediatric cases reported during the pediatric exclusivity period.

Table 3: Characteristics of pediatric cases reported during the pediatric exclusivity period (n=5)	
Gender [n=4]	Male: 1 Female: 3
Age [n=5]	13 years: 1 14 years: 1 15 years: 1 16 years: 2
Origin [n=5]	US: 5
Event date [n=3]	2005: 2 2006: 1
Duration of therapy (# of gemcitabine cycles) [n=4]	Average: 2.5, Median: 2 Range: 1 to 5
Indications [n=5]	Osteosarcoma: 3 Renal medullary carcinoma: 1 Hodgkin lymphoma: 1
Outcomes [n=5]	Death = 1 Hospitalization = 2 Other = 2

4.2 Summary of Cases received during the 1-year post-pediatric exclusivity period.

The raw number of pediatric cases received during the 1-year post-pediatric exclusivity period was nine. Of the nine cases, there were five unduplicated pediatric cases (three were incorrectly submitted/coded adult cases, one was a duplicate). The five cases are described below. Unlabeled events for gemcitabine are underlined.

- One of the five cases reported death as an outcome.

ISR# 4655490-6; MD; Literature Report, Fatal

A 15-year old female with renal medullary carcinoma received five cycles of cisplatin, paclitaxel, gemcitabine, and pegfilgrastim with reduction of volume of lesions and resolution of lymphadenopathy. She experienced grade 2 nausea, grade 3 neutropenia, grade 3 thrombocytopenia, grade 3 anemia, and renal toxicities including grade 3-4 hypomagnesemia, grade 4 hypokalemia, and grade 2 hypophosphatemia (common terminology criteria for adverse events v3.0). She also developed moderate high-frequency hearing loss² after the fifth cycle and amifostine was given prior to the cisplatin for cycle 6. The hearing loss worsened and carboplatin was substituted for cisplatin. After cycle two with carboplatin she had progressive disease. She received one cycle of methotrexate, vinblastine, and doxorubicin. Her disease progressed and she died in a hospice program 15 days later, nearly ten months after her diagnosis.

² Labeled for neurohearing toxicity

- The remaining four cases are non-fatal reports. All reports are from the United States. Cases are confounded by concomitant medications and recent surgical procedures. Table 4 below describes the cases.

Table 4: Summary of non-fatal cases reported during the pediatric exclusivity period.

ISR #	Age(yr)/ Sex	Source	Indication	ADR	Comments
4724539-4	13/F	MD	metastatic osteosarcoma	cellulitis at surgical site	s/p limb salvage with prosthesis and revision, also suspect docetaxel
4806873-2	16/M	MD	osteosarcoma	<u>hypoxia</u> ³ , pneumonitis, dyspnea	also suspect docetaxel
4827738-6	16/?	TX	osteosarcoma	<u>mucositis</u> , <u>pancytopenia</u> ⁴	literature report
4893525-6	14/F	MD	Hodgkin lymphoma	increased alanine aminotransferase	also suspect vinorelbine

5. Review of Fatal Pediatric Gemcitabine Cases

A search of AERS was performed 2/27/2006 to identify all fatal pediatric cases associated with gemcitabine before the pediatric exclusivity period. The raw number of fatal pediatric cases associated with gemcitabine in AERS was six. Of the six cases, there was one unduplicated pediatric case (four were incorrectly submitted/coded adult cases, one was a duplicate). Details of this case are below. Unlabeled events for gemcitabine are underlined.

ISR# 3969083-7; — fatal

A 9-year old female with refractory acute lymphoblastic leukemia received her first dose of gemcitabine 8/19/2002. She had four prior “multiagent” chemotherapy regimens and multiple bone marrow and CNS relapses. Baseline performance scale was 80 (scale used not specified). She was persistently febrile and was covered with broad-spectrum antimicrobials. On day 5 after gemcitabine administration she complained of leg pain and a morphine infusion was started. Her WBC count was 1.0 with 69% circulating blasts (baseline WBC 4.7 with 88% blasts). The patient continued to be febrile and had frequent nosebleeds. She had several episodes of vomiting with coffee ground material and received frequent platelet transfusions for refractory thrombocytopenia. On day 8 she developed respiratory distress³ and required oxygen. Chest x-ray showed bilateral “fluffy” infiltrates. Her WBC count was 4.4 with 85% blasts. The differential diagnosis for acute respiratory distress³ included bacterial or fungal pneumonia, pulmonary hemorrhage³, or leukemic involvement. The family requested discontinuation of gemcitabine and the patient received comfort measures only. The patient died 2 days later (—)

³ Labeled for pulmonary toxicity (including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema and acute respiratory distress syndrome)

⁴ Labeled for myelosuppression

6. Summary/Recommendations

The AERS database was searched for adverse events associated with gemcitabine in pediatric patients occurring during the pediatric exclusivity period. During this period, one case reported death as an outcome due to disease progression. Most of the remaining cases reported labeled adverse events, including cellulitis, pneumonitis, pancytopenia⁵ and hepatotoxicity. One case reported an unlabeled adverse event, mucositis, an adverse event commonly associated with chemotherapy.

An additional search of AERS was performed to identify all fatal pediatric cases associated with gemcitabine before the pediatric exclusivity period. This search yielded one other unduplicated fatal pediatric case. This case described a patient with acute lymphoblastic leukemia with fever, leg pain, decreased white blood cells, hematemesis, epistaxis, refractory thrombocytopenia and acute respiratory distress. The family of this patient requested comfort measures only and she died 2 days later (cause of death not specified). Although these adverse events had a temporal relationship to the administration of gemcitabine, most of the events were labeled events for gemcitabine in a heavily pretreated refractory patient. Unlabeled events included epistaxis and hematemesis, clinical manifestations commonly seen in cancer patients with thrombocytopenia.⁶

This review did not identify any notable or unexpected safety concerns with the use of gemcitabine in pediatric patients. Note that the pediatric patients in this case series were all adolescents. DDRE continues to routinely monitor reports of adverse events with the use of gemcitabine in pediatric patients.

⁵ Labeled for myelosuppression

⁶ DeSancho MT, Rand JH. Coagulopathic Complications of Cancer Patients. In: Holland-Frei Cancer Medicine: Kufe DW et al (eds.) 2003 BC Decker Inc, Spain. Accessed online 3/28/06 <http://online.statref.com/document.aspx?fxid=72&docid=2044>.

Appendix

Drug Product Information

The product labeling for gemcitabine includes the following information concerning pediatric patients.

The effectiveness of Gemzar in pediatric patients has not been demonstrated. Gemzar was evaluated in a Phase 1 trial in pediatric patients with refractory leukemia and determined that the maximum tolerated dose was 10 mg/m²/min for 360 minutes three times weekly followed by a one week rest period. Gemzar was also evaluated in a Phase 2 trial in patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) using 10 mg/m²/min for 360 minutes three times weekly followed by a one week rest period. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation, which were similar to those reported in adults. No meaningful clinical activity was observed in this Phase 2 trial.

Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

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/s/

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